Recent advances in hybrid quantum-chemical approaches for free energy simulations and constant pH simulations

Bernard R. Brooks , Gerhard König, and Juyong Lee

Laboratory of Computational Biology,
National Heart, Lung, and Blood Institute,
National Institutes of Health

This presentation focuses on our recent efforts to develop practical and efficient quantum based methods for calculating solvation free energies[1] and extending those to constant pH simulations using explicit waters and discrete charges with advanced replica-exchange methods [2]. The basic idea is to perform a series of inexpensive simulations, or coupled set of simulations, on an classical potential energy surface and then to connect those simulations to a quantum mechanical potential energy surface[3], providing free energies of the much more expensive quantum or QM/MM system. Difficulties in making the connection between potential energy surfaces will be discussed and a complex multi-step approach will be presented that allows accurate results to be obtained at modest cost.

These approaches can be combined with both enhanced sampling techniques that preserve the canonical ensemble and or efforts to improve multi-scale macromolecular modeling methods and to apply them to problems in structural biology and biophysics. Applications in biophysics have focused on the use of constant-pH simulations methods and novel replica exchange methodology. Basic concepts will be presented for:
-- Predicting hydration free energies with a hybrid QM/MM approach.
-- Free energy costs of applying constraints to quantum or QM/MM simulations.
-- pH replica exchange - replica exchange in pH space using discrete protonation states.
-- Double Reservoir pH-REX – A high and a low pH reservoir to investigate pH dependence.
-- Constant pH simulation using enveloping distribution sampling (EDS) with replica exchange.
-- Combining Hamiltonian and temperature based or SGLD based replica exchange methods.

[1] König, G., Miller, B. T., Boresch, S., Wu, X., and Brooks, B. R.; Enhanced Sampling in Free Energy Calculations: Combining SGLD with the Bennett's Acceptance Ratio and Enveloping Distribution Sampling Methods, *Journal of Chemical Theory and Computation*, **2012**, 8, 3650-3662.

[2] Itoh SG, Damjanovic A, Brooks BR. pH replica-exchange method based on discrete protonation states, *Proteins*, **2011**, 79(12), 3420-36.

[3] König, G., Pickard, F. C., Mei, Y., and Brooks, B. R.; Predicting hydration free energies with a hybrid QM/MM approach, An evaluation of implicit and explicit solvation models in SAMPL4, *J. Comput. Aided. Mol. Des.*, **2014**, in press.